Attorney Docket # 5403-2RCE

Patent

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of
Stefan Lukas et al.
Serial No.: 09/177,427
Filed: October 22, 1998
For: Taste Masked Pharmaceutical Compositions

Examiner: Gregory W. Mitchell
Group Art: 1617

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Kent H Cheng
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P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

SIR:

This is an appeal, pursuant to 37 C.F.R. §1.192(a) from the decision of the Examiner in the above-identified application, as set forth in the Final Office Action wherein the Examiner finally rejected appellant's claims. The rejected claims are reproduced in the Appendix A attached hereto. A Notice of Appeal was filed on March 3, 2005. This Appeal Brief is being submitted in triplicate.

The fee of $500.00 for filing an Appeal Brief pursuant to 37 C.F.R. §1.17(f) is submitted herewith. A three-month extension fee of $1020 is also submitted. Any additional fees or charges in connection with this application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

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02 FC:1253 1020.00 OP

I. REAL PARTY IN INTEREST

The assignee, FH Faulding & Co. Limited, is the real party of interest in the above-identified U.S. Patent Application.

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals and/or interferences related to the above-identified application at the present time.

III. STATUS OF CLAIMS

Claims 16-30 have been rejected. Claims 16-30 are on appeal.

IV. STATUS OF AMENDMENTS

An Amendment with a request for reconsideration was filed on January 4, 2005 subsequent to the Final Office Action dated October 4, 2004.

In response, on February 8, 2005 the Examiner entered an Advisory Action maintaining the rejection of the pending claims.

V. SUMMARY OF THE INVENTION

Appellant's Appellants' invention is directed to a pharmaceutical formulation comprising:

spray dried powder particles having a core element containing one or more pharmaceutically active compounds and a substantially continuous polymeric coating thereon, both to taste mask and to

provide sustained release of said one or more active compounds wherein the polymer coating comprises less than 23% by weight of the formulation, wherein said core has an aspect ratio of less than 3 and further wherein no more than 25 wt.-% of the particles are less than 25 micrometers and no more than 2 wt.-% of the particles are over 250 micrometers.

VI. ISSUES

1. Whether claims 16 to 25 and 27 to 30 are patentable under 35 U.S.C. §103(a) over CA 2,068,366 to Morella et al. ("CA '366") in view of U.S. Patent No. 5,635,200 to Douglas et al. ("Douglas")?

2. Whether claim 26 is patentable under 35 U.S.C. §103(a) based on the combination of CA '366 in view of Douglas and further in view of U.S. Patent No. 4,808,411 to Lu et al. ("Lu") or U.S. Patent No. 5,707,646 to Yajima et al. ("Yajima")?

VII. GROUPING OF CLAIMS

The pending claims are 16-30, of which claims 16 and 27 are independent. All the claims stand or fall together.

VIII. ARGUMENT

A. Obviousness Rejection Based on CA '366 and Douglas

The present invention is a pharmaceutical formulation. Prior to the present invention, the preferred method of production of microcapsules was by spray drying from a solution. However that method would not produce a coating powder having the needed sustained release properties.

Applicants have demonstrated that the powders of the present invention provide the preferred sustained release properties when compared to the closest coated product found in the prior art. The sustained release properties of the present invention are evidenced by the rate of dissolution of the presently claimed spray dried drug particles shown in the Declaration of Stefan Lukas and by the bioavailability study shown in Table 2 of the present specification. Accordingly, the present invention provides a significant improvement over the prior art.

Applicants discovered that the presence of "fine" drug particles leads to an increased rate of drug release after coating with a polymer. This was thought to be due to the increased drug surface area that in turn led to a thinner polymer coating when common amounts of polymer were utilized. Initially, the Applicants thought (as did others in the art) that control of drug particle size was the only important factor. Applicants subsequently discovered that particle shape was potentially an important parameter. Two test batches, D4426 and D4427, were treated to determine the effect of needle shaped particles. Attached to the enclosed (and previously submitted) Lukas Declaration are electron micrographs of powder of test batches D4426 and D4427. Batch D4426 was utilized as supplied by the supplier. As can be readily seen from the electron micrograph in Batch D4426 (which details the material provided by the supplier), a certain number of particles are effectively oblong in shape and contain sharp edges and are outside the now claimed aspect ratio. In contrast, the electron micrograph of Batch D4427 does not demonstrate particles with these dimensions.

Further, a more homogenous particle size distribution also improves the performance characteristics. When these batches of particles were subjected to the process described, it was found that the needle shaped particles produced a material where 19% of the material was released after 40 minutes, which is unacceptably high. In contrast, the more homogeneous batch D4427 only

demonstrated 8% release after 40 minutes, an acceptable release profile. The results of these trials are discussed in the enclosed Lukas Declaration.

The Office Action dated October 23, 2003 asserts that CA '366 essentially shows every feature of the invention as defined in claims 16 to 25 and 27 to 30 but for the aspect ratio of less than 3. Applicants respectfully disagree.

The Examiner cites to page 4, lines 15 to 23, and contends that the reference shows that the coating of the dosage form can be from 10 to 80% of the formulation. However, such statements cannot be taken alone out of context from this multipage document. For example, at page 15, line 16 to 26, the reference lists the different parameters which are involved to obtain a microcapsule coating composition with a particular release profile for the material. These parameters include controlling during the process of making the composition the temperature, solvent concentration, spray dryer capacity, atomizing air pressure, droplet size, viscosity, total air pressure and selection of solvent system. According to CA '366, these parameters will allow the formation of a range of coatings on the particles, ranging from dense, continuous, non-porous coats through to more porous microcapsule/polymer matrices. In view of this extensive list of parameters, it is submitted that while the reference may use broad language to describe the wt. % of the coating, the Examiner must consider the entire reference, and particularly the release rate of the drug over time.

The Examiner cites to Example 1 of CA '366 with less than 30% released in 40 minutes as one basis to show that the prior art teaches a method of preparing a coating powder having sustained release properties. See page 3 of Office Action dated October 4, 2004. However, as discussed in the Lukas Declaration, such an upper limit in release rate would cover unacceptable release rates necessary for a sustained release formulation. As noted in the Lukas Declaration, about 8% of the

drug should be released after 40 minutes for acceptable sustained release properties. See paragraph 13 of the Lukas Declaration.

The Examiner additionally cites to Example 5 of CA '366 as descriptive of the release rate and taste masking of the compositions claimed in CA '366. Example 5 shows compositions prepared using 28% coating agent, and compares the compositions prepared when the drying agent is dry air and when the drying agent is ambient air. The Examiner notes from Figures 5 (a) and (b) that "the coating of the composition prepared utilizing dry air as the drying agent is smooth, whereas the composition prepared utilizing ambient air is porous." The Examiner further notes from Figure 6 that "it is shown that the use of dry air as the drying gas produces a composition with a release rate about half of that of a composition prepared utilizing ambient air." A closer review of Figure 6 indicates that the lower release rate of the composition prepared utilizing dry air results in about 18% of the drug being release after 40 minutes. As discussed in the Lukas Declaration, such a release rate of the drug is unacceptably high for a sustained release formulation. See paragraph 13.

The Examiner cites Douglas to provide the teaching of the aspect ratio of less than 3. While the Examiner may be relying on Douglas only for the discussion of the aspect ratio or physical shape of the particles used by Douglas, it is submitted that the command of 35 U.S.C. §103 requires that the entirety of the reference be considered. In this regard, it should be noted that Douglas provides absolutely no information as to the dissolution characteristics of his dosage forms. That is to say, one cannot tell whether those dosage forms are sustained release, controlled release or immediate release products. Douglas' disclosure as to the weight ranges for the lipid and for the binder make it clear that a product according to Douglas could not have a coating weight of 23 wt.-% or less.

Further neither CA '366 nor Douglas provides any motivation for one of ordinary skill in the art to combine the two references so as to render obvious the presently claimed invention. The Examiner states that motivation to combine is "because each of the invention [of the cited references] is drawn to a formulation comprising a coated particle and is directed to an invention where the masking of tastes is required." See page 7 of the Office Action dated October 4, 2004. Douglas states that "the presence of irregular shaped particles reduces the effectiveness of subsequent overcoating procedures in masking the bitter taste of the drug" (col. 5, lines 9-12). CA '366 only discussion of an overcoating process consists of applying a wax seal and a polymer coating onto the drug core thereby producing a product with improved taste masking compared to the polymer coating alone. See Example 7 and Figure 8. There is no motivation to further modify the process described in CA '366 with the disclosure of Douglas to further improve taste masking. Further, the combination of CA '366 and Douglas provides no indication of whether or not avoiding irregular shaped particles would be successful in providing the presently claimed pharmaceutical formulation that masks the taste of the drug and provides sustained release of the drug.

The obviousness rejection involving CA '366 and Douglas is based on an impermissible "obviousness to try" standard. See in re O'Farrell, 7 U.S.P.Q. 2d 1673, 1680-1681 (Fed. Cir. 1988), which states as follows:

> "Any invention that would in fact have been obvious over §103 would also have been, in a sense, obvious to try. The question is: when is an invention that was obvious to try nevertheless nonobvious? The admonition that 'obvious to try' is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been 'obvious to try' would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful. E.g., In re Geiger, 815 F. 2d at 688, 2

USPQ 2d at 1278; Novo Industri A/S v. Travenol Laboratories, Inc. 677 F.2d 1202, 1208, 215 USPQ 412, 417 (7th Cir. 1982); In re Yates, 663 F.2d 1054, 1057, 211 USPQ 1149, 1151 (CCPA 1981); In re Antonie, 559 F.2d at 621, 195 USPQ at 8-9."

As noted above, many process parameters in making the composition effect the coating of the final spray dried powder drug particles, including the temperature, solvent concentration, spray dryer capacity, atomizing air pressure, droplet size, viscosity, total air pressure and selection of solvent system. It is not clear from the teaching of CA '366 which parameter is critical and what characteristics of the final spray dried powder drug particles are necessary to result in acceptable taste masking and acceptable sustained release rates. Douglas does not remedy the deficiencies of CA '366, as no direction is provided that aspect ratio is important to allow for acceptable taste masking and acceptable sustained release rates.

It is therefore respectfully submitted that one of ordinary skill in the art would not consider combining CA '366 and Douglas, and this combination merely would at most render the claimed invention "obvious to try." Accordingly, it is respectfully requested that the rejection of claims 16 to 25 and 27 to 30 under 35 U.S.C. §103(a) over CA '366 in view of Douglas be withdrawn.

C. Obviousness Rejection Based on the CA'366, Douglas and U.S. Patent 4,808,411 or U.S. Patent 5,707,646

Claim 26 has been rejected under 35 U.S.C. §103(a) based on the combination of CA '366 in view of Douglas and further in view of U.S. Patent No. 4,808,411 to Lu et al. ("Lu") or U.S. Patent No. 5,707,646 to Yajima et al. ("Yajima"). It is submitted that this rejection is also improper and should be withdrawn.

As stated by the Examiner, Lu and Yajima are relied on "to show that it is desirable to mask the taste of and achieved sustained release of clarithromycin" (page 8 of Office Action of October 4, 2004).

As discussed above, the combination of CA '366 and Douglas does not render obvious the presently claimed pharmaceutical formulation or the method of preparing the same. The addition of Lu or Yajima does not provide teaching that would lead one of ordinary skill to the claimed pharmaceutical formulation, let alone the claimed pharmaceutical formulation wherein the active is clarithromycin.

Nothing in the Examiner's discussion of the Yajima or Lu references or in either of the references indicates that a substantially continuous polymer coating is formed and that the resulting product has sustained release properties or that the coating comprises less than 23% by weight of the formulation.

The Lu reference discloses a complex of carbomer (acrylic acid polymers) and erythromycin or a derivative thereof. Lu's compositions are prepared by dispersing the drug, such as erythromycin, in a suitable organic solvent such as ethanol or acetone, and dispersing the carbomer separately in ethanol, mixing the two solutions slowly to allow formation of the reaction product and then evaporating most of the solvent and diluting the solution with water. The reaction product is recovered by filtration and is then dried. No mention is made of spray drying or spray dried particles. This reference gives no indication of the weight percent of the coating.

Yajima relates to a taste masked pharmaceutical formulation comprising clarithromycin but is no more pertinent than Lu as discussed above.

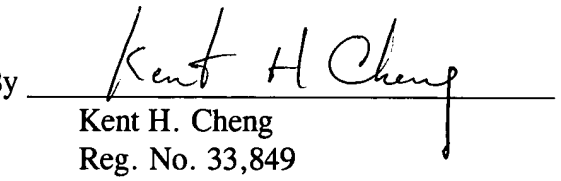
It is therefore respectfully submitted that one of ordinary skill in the art would thus not consider combining CA '366, Douglas and Lu or Yajima. Accordingly, it is respectfully

requested that the rejection of claim 26 under 35 U.S.C. § 103 based on the combination of CA '366 in view of Douglas and further in view of Lu or Yajima be withdrawn.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that appellant's claims are not rendered obvious by the cited references and are, therefore, patentable over the art of record, and the Examiner's rejections should be reversed.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By 

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Dated: July 14, 2005

APPENDIX

16. A pharmaceutical formulation comprising: spray dried powder particles having a core element containing one or more pharmaceutically active compounds and a substantially continuous polymeric coating thereon, both to taste mask and to provide sustained release of said one or more active compounds wherein the polymer coating comprises less than 23% by weight of the formulation, wherein said core has an aspect ratio of less than 3 and further wherein no more than 25 wt.-% of the particles are less than 25 micrometers and no more than 2 wt.-% of the particles are over 250 micrometers.

17. The pharmaceutical formulation according to claim 16 wherein said core has an aspect ratio from about 1 to about 2.

18. The pharmaceutical formulation according to claim 16 wherein said core an aspect ratio of about 1.

19. The pharmaceutical formulation according to claim 16 wherein said core is substantially spherical.

20. The pharmaceutical formulation according to claim 16 wherein said core element has a particle size of between 0.1 μm and 250 μm.

21. The pharmaceutical formulation of claim 20 wherein said particle size is in the range of 35 μm and 175 μm.

22. The pharmaceutical formulation of claim 16 wherein said coating comprises less than 20% of the weight of the formulation.

23. The pharmaceutical formulation according to claim 16 wherein said polymeric coating is an ethyl cellulose coating.

24. The pharmaceutical formulation of claim 16 wherein the thickness of said coating is within the range of about 0.005 to 25 μm.

25. The pharmaceutical formulation of claim 16 wherein said pharmaceutically active compound is paracetamol.

26. The pharmaceutical formulation of clam 16 wherein said pharmaceutically active compound is clarithromycin.

27. A method of preparing a formulation of spray dried powder particles having a core element containing one or more pharmaceutically active compounds and a substantially continuous polymeric coating thereon, both to taste mask and to provide sustained release of said one or more active compounds where the polymer coating comprises less than 23% by weight of the formulation the method comprising:

mixing said core element and said coating in a diluent to form a mixture; and

spray drying said mixture to form a powder wherein said core has an aspect ratio of less than 3 and wherein no more than 25 wt.-% of particles are less than 25 micrometers and no more than 2 wt.-% of particles are over 250 micrometers.

28. The method of claim 27 wherein said core has an aspect ratio of from 1 to 2.

29. The method of claim 27 wherein said core has an aspect ratio of about 1.

30. The method of claim 27 wherein said core is substantially spherical.

THE COMMISSIONER OF PATENTS
01 November 2001

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Applicant: S Lukas et al Examiner: Alysia Berman

Serial No.: 09/177,427

Title: Taste Masked Pharmaceutical Compositions

DECLARATION UNDER 37 C.F.R. Si. 132

Hon. Commissioner of Patents
and Trade Marks
Washington, DC 20231

Sir,

I, Stefan Lukas, declare and say as follows:

1. I am an inventor of the subject matter claimed in the above-identified U S patent application Serial No. 09/177,427.

2. I hold a Masters in Applied Science from the University of South Australia which was conferred in 1988. I have worked for F H Faulding & Co Limited since April 1988. I was first involved in spray drying in 1988 with what was at the time a minor research project looking at microencapsulation using a lab-scale spray dryer. As part of this program I developed the basic polymer coating process and formulation from concept to pilot scale manufacture eventually using pilot equipment on site at Niro Atomiser, Soborg, Denmark. After two separate visits to the pilot facility in Denmark two different formulations were successfully scaled up and taken through to commercial reality.

3. I identified the critical formulation constraints not previously described in the literature. During more than 8 years continuous hands on experience in all aspects of spray drying micro encapsulation I thoroughly investigated raw material specifications/requirements, requirements of coating systems, atomisation (including evaluation of numerous atomisation techniques both physical and electrostatic), evaluated the drying environment and the importance of the composition and physical attributes of the drying gas.

4. I also liaised with an extra mural team at Particle Coating Technologies (PCT) in St Louis, Missouri in the development of a taste masking process that involved spray congealing of molten wax compositions. In this process the active actually dissolved in the molten wax producing a different kind of spray dried microencapsulated particle. I have read extensively in the area and have attended several drying symposia.

5. I have read and am familiar with the Office Action mailed 8 May, 2001, in respect of application Serial No. 09/177,427, and make this Declaration in support of the patentability of the claims in the above-identified application.

6. As set forth in the specification of the application, Serial No. 09/177,427 and as recited in the claims, the invention is directed towards a taste masked pharmaceutical composition. The claimed composition has a number of properties, one property is that the polymer coating comprises less than 23% by weight of the formulation. A further property is that the core has an aspect ratio of less than 3. A final property included within the claims is the fact that the particle

size is controlled within a prescribed range so that only a certain percentage of particles are present as 'large' or 'fine' particles. I note that no more than 25% w/w of particles are less than 25 micrometres and no more than 2% w/w of particles are over 250 micrometres. As also described, the invention further relates to a method of preparing a formulation of the invention comprising spray drying powder particles with a suitable aspect ratio to produce a formulation with acceptable properties.

7. I note in the Office Action that the Examiner is of the opinion that the limitations of the aspect ratio of less than 3 (as enclosed in claim 16) and/or the substantially spherical nature of the core (as disclosed in claim 19) is not considered critical and does not render the claims patentable over the prior art.

8. Whilst I understand how the Examiner could reach this position, I respectfully disagree with this view on the basis of my research toward the invention.

9. An important feature of the particles of the present invention is the particle shape. In developing the claimed process, a number of trial batches were run in order to produce a pharmaceutical composition with acceptable product qualities. We had observed, for example, that when the process of CA2068366 was carried out, some of the batches appeared to be acceptable whereas other were clearly unacceptable. We therefore wanted to conduct research to improve the consistency of the product produced.

10. In tests to determine the critical factors, we particularly looked at a number of variables such as particle size and particle shape. Merely by way of overview, we noted that where there was a high occurrence of "fine" drug particles, there was an increased rate of drug released after polymer coating. Whilst not wishing to be bound by theory, we thought that the smaller particles increased the drug surface area which in turn, led to a thinner polymer coating. At least in a theoretical manner, one can easily see that if there is a great number of drug particles that are too small, the surface area to drug ratio with be high, leading to a thinner coating. Accordingly, whilst the process works with fine particle, it is preferable that the size of the particles be controlled within a certain range. My recollection in developing this process is that it was this observation that led to the limitation that appears as a preferred embodiment in claims 20 and 21 of the present application.

11. With respect to particle shape, we conducted a number of tests to determine if particle shape affects the process of invention as it was not expected to. These tests were predominantly influenced by the observation that with certain batches, unacceptable taste masking was observed whereas with certain other batches, taste masking was adequate. Indeed, our review of literature in this area provided no indication as to what caused this variation. Indeed, we noted when running the process of the cited prior art documents, that some batches appeared to produce acceptable results whereas others were unacceptable.

12. Whilst a number of trials were run to determine the source of this variation, two spring immediately to mind. I have reviewed my files and have located test batches D4426 and D4427. Attached as Exhibit 1, is a Scanning Electron Micrograph (SEM) of the drug particles used in test D4426. Attached as Exhibit 2, is a SEM of the drug particles used in test D4427. These two materials were then subjected to the spray drying process using identical amounts of solvent and identical process conditions.

13. The test results demonstrate that there was significant difference between the dissolution rates of the two batches. The batch containing needles (i.e. an aspect ratio in excess of 3), was tested and observed that 18% of the material was released after 40 minutes. For the purpose of sustained release, this was found to be a less preferred dissolution profile. In contrast, using the material with an aspect ratio of less than 3, only 6% was released after 40 minutes. Accordingly, we were able to ascertain that the presence of "needle" shaped particles led to unacceptably high rates of drug release. Whilst not wishing to be bound by theory, I am of the opinion that the higher

release rate can be explained by the increased surface area inherent in a needle particle and possibly also, the tendency of premature breaking of the polymer coat at the vertices of these particles (where the polymer coating would be thinner and under greater stress).

14. In essence, drug release from a coated particle is dependent on the thickness and quality of the polymer coating. In turn, the thickness of the polymer coating is dependent on the specific surface area of the drug particles to be coated. We have found that the specific surface area is controlled within acceptable boundaries to give acceptable sustained release profiles by increasing the particle size and reducing the aspect ratio (as claimed in the application). In addition, this minimises the stress fractures that appear to be deleterious to the integrity of the coating layer. Accordingly, I consider that the combination of particle size distribution and aspect ratio of the material to be coated is crucial to acceptable produce performance. In addition, as far as I am aware, prior to the experimental work done, this was not a known feature of this process.

15. I have read, and am familiar with, CA2068366. I note, as acknowledged by the Examiner, that no particular shape is given in this citation. It does not appear to me that the authors were aware of the crucial nature of the shape of the particles and the particle size distribution at the time of the filing. It is for this reason that this document does not disclose the importance of the aspect ratio or shape.

16. I have read and am familiar with US 4,808,411. Once again, as noted by the Examiner, this reference does not disclose the crucial feature of the shape of the particle. This is not surprising as as stated previously, this was not known at the time of the publication.

17. Accordingly, I consider the present invention to contain patentable matter over and above the disclosure in the cited prior art. I consider that the determination of a suitable aspect ratio, shape and particle size distribution that guarantees acceptable taste masking and sustained released properties to be a patentable invention over the art. A worker following the directions in the art, would at best, only have a chance of reproducibly producing an acceptable product. This would only occur if the worker were fortuitously to select a core material with suitable aspect ratios and particle size distribution. The advance provided by the present application is that a worker can now proceed with certainty to achieve a product with acceptable product performance. By providing teachings that allow a skilled addressee to determine whether this performance will be achieved, the present inventors have provided for greater product output and better compliance with drug dissolution profiles. Accordingly, I consider there is a patentable advance and disagree with the Examiner on this point.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Act, and that such wilful false statements may jeopardise this application or any patent issuing thereon.

Dated 1/11/01

Stefan Lukas

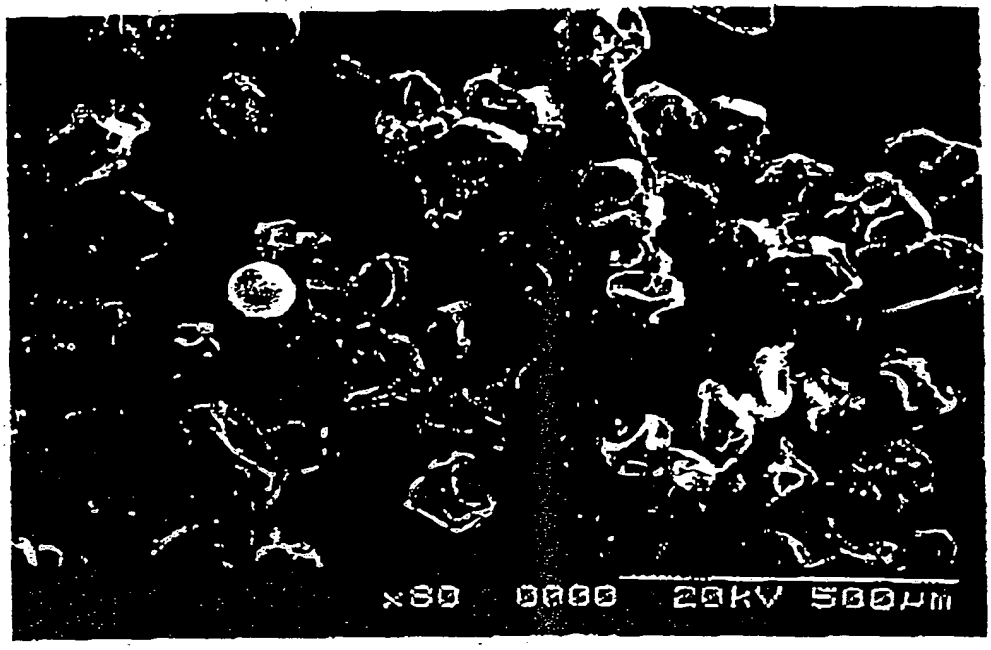
THE COMMISSIONER OF PATENTS
01 November 2001

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Applicant:	S Lukas et al	Examiner:	Alysia Berman
Serial No.:	09/177,427		
Title:	Taste Masked Pharmaceutical Compositions		

Attached hereto is exhibit – 1 referred to in the declaration of Stefan Lukas dated 2 November 2001.

Electronmicrograph of powder batch D4426 (batch containing 'needle' shaped particles)



THE COMMISSIONER OF PATENTS
01 November 2001

IN THE UNITED STATES PATENT AND TRADE MARK OFFICE

Applicant:	S Lukas et al	Examiner:	Alysia Berman
Serial No.:	09/177,427		
Title:	Taste Masked Pharmaceutical Compositions		

Attached hereto is exhibit – 2 referred to in the declaration of Stefan Lukas dated 2 November 2001.

Electronmicrograph of powder batch D4427 (batch where 'needle' shaped particles were removed by sieving)